Page 22, replace the paragraph bridging lines 13-19 with the following new paragraph:

-- Using the transfected HCN cells, the effect of various concentrations of the substance zatebradine, which is known as an I_f blocker, were examined. The inhibition by zatebradine was calculated from the relative change in fluorescence from the time 60 seconds. For each concentration of the inhibitor, the mean of in each case 6 wells of the microtiter plate was determined. From these values, the IC50 of zatebradine was calculated as 26 μM, a value which corresponds well with the value of 31 μM determined electrophysiologically in the same cells.--

Delete the paragraph bridging page 22, line 21 through page 23, line 3.

REMARKS

By this Preliminary Amendment, the specification is amended to delete references to any figures and to correct minor typographical errors. In a Notice of Incomplete Nonprovisional Application mailed by the PTO in the parent application, the Office stated that this application was filed without figures. Applicants have reviewed the parent application and concluded that figures are not necessary in order for one of skill in the art to understand and make and use the invention. Therefore, Applicants have removed all references to the figures in the text of the specification. No new matter is added by this Preliminary Amendment.

A Petition in support of this Preliminary Amendment is attached hereto, along with the required fee under 37 C.F.R. § 1.17(h) of $130.00.

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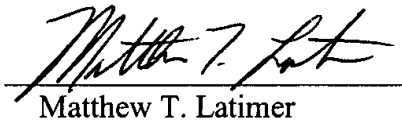
If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: 

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Attachment:
Appendix

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APPENDIX ACCOMPANYING PRELIMINARY AMENDMENT

Rule 53(b) Continuation of 09/779,587

IN THE SPECIFICATION:

Please amend the specification as follows:

Page 3, replace the paragraph bridging lines 15-28 with the following new paragraph:

-- Generally speaking, the present invention provides a process for examining hyperpolarization-activated cation channels. In the process, cells that express the hyperpolarization-activated cation channels are hyperpolarized [B] (i.e. the hyperpolarization-activated cation channel is activated) [B] and this hyperpolarization of the cells, which is reversed under physiological conditions by the activity of the hyperpolarization-activated cation channel, is maintained. By exclusion of extracellular sodium ions, the activated channel is unable to transport sodium ions into the cells, i.e. to depolarize the cells. If, simultaneously or even prior to the addition of the sodium ions, substances are added that modulate the activity of the hyperpolarization-activated cation channel, the depolarization is affected. For example, compared to when only sodium ions are added, depolarization is increased in the case of HCN activators (for example forskolin) and reduced in the case of HCN inhibitors (for example zatebradine = 3-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one; Reiffen et al. (1990)).--

Page 11, replace the paragraph bridging lines 4-11 with the following new paragraph:

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-- The cells can, but do not necessarily, contain nucleic acids (i.e., RNA, DNA, PNA) that [codes] code for the hyperpolarization-activated cation channel. In embodiments, the cells contain DNA. In embodiments, the cells contain RNA. In embodiments, the cells contain a cDNA of a hyperpolarization-activated cation channel in a suitable plasmid. Such cells can be prepared by transfecting the original cell line with a plasmid that contains the cDNA of a hyperpolarization-activated cation channel. Other techniques can be used as well. Techniques for introducing heterologous nucleic acids into cells are well known and widely practiced by those of skill in the art, and thus need not be detailed here.--

Page 15, replace the paragraph bridging lines 12-20 with the following new paragraph:

-- In the FLIPR, Na^+ is added to the cells, so that the activated HCN (after a few seconds, in which there are mixing effects) causes, from about 15 seconds after the addition of Na^+, depolarization of the cells, which becomes visible by an increase in fluorescence. The detection of HCN modulators can rely on a difference between cells having an activated HCN channel (e.g., only Na^+ addition) and cells having a blocked HCN channel (e.g., Na^+ + 8 mM CsCl). It has been determined that a greater difference provides a greater reliability in the system. For example, activation of the HCN channel by pre-incubation with 10 μM forskolin increases the difference between the uninhibited 100% value from the inhibited 0% value considerably[(see Fig. 1)].--

Page 21, replace the paragraph bridging lines 7-15 with the following new paragraph:

-- In the FLIPR, Na^+ is added to the cells so that the activated HCN (after a few seconds, in which there are mixing effects) causes, from about 15 seconds after the addition of Na^+,

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depolarization of the cells, which becomes visible by an increase in fluorescence. An activation of the HCN channel by preincubation with 10 μM forskolin increases the difference between the uninhibited 100% value from the inhibited 0% value considerably [(see Fig. 1; discussed further below)]. By comparison with the control values, it can be detected whether a substance to be tested is an activator (more rapid or more pronounced depolarization) or an inhibitor (slower or inhibited depolarization[, see Fig. 2: effect of zatebradine]).--

Page 22, replace the paragraph bridging lines 13-19 with the following new paragraph:

-- Using the transfected HCN cells, the effect of various concentrations of the substance zatebradine, which is known as an I_f blocker, were examined[(see Fig. 2; discussed further below)]. The inhibition by zatebradine was calculated from the relative change in fluorescence from the time 60 seconds. For each concentration of the inhibitor, the mean of in each case 6 wells of the microtiter plate was determined. From these values, the IC50 of zatebradine was calculated as 26 μM, a value which corresponds well with the value of 31 μM determined electrophysiologically in the same cells.--

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